Peripheral chemoreceptor control of cardiovascular function at rest and during exercise in heart failure patients

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1Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; 2Women and Children’s Health Research Institute, University of Alberta, Edmonton, Alberta, Canada; 3Cardiovascular and Stroke Research Centre (ABACUS), Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; 4Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Alberta, Canada; and 5G.F. MacDonald Centre for Lung Health (Covenant Health), Edmonton, Alberta, Canada

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Edgell H, McMurtry MS, Haykowsky MJ, Paterson I, Ezekowitz JA, Dyck JR, Stickland MK. Peripheral chemoreceptor control of cardiovascular function at rest and during exercise in heart failure patients. J Appl Physiol 118: 839–848, 2015. First published January 22, 2015; doi:10.1152/japplphysiol.00898.2014.—Peripheral chemoreceptor activity/sensitivity is enhanced in chronic heart failure (HF), and sensitivity is linked to greater mortality. This study aimed to determine the role of the peripheral chemoreceptor in cardiovascular control at rest and during exercise in HF patients and controls. Clinically stable HF patients (n = 11; ejection fraction: 39 ± 5%) and risk-matched controls (n = 10; ejection fraction: 65 ± 2%) performed randomized trials with or without dopamine infusion (2 μg·min⁻¹·kg⁻¹) at rest and during 40% maximal voluntary contraction handgrip (HG) exercise, and a resting trial of 2 min of inspired 100% oxygen. Both dopamine and hyperoxia were used to inhibit the peripheral chemoreceptor. At rest in HF patients, dopamine decreased ventilation (P = 0.02), decreased total peripheral resistance index (P = 0.003), and increased cardiac and stroke indexes (P ≤ 0.01), yet there was no effect of dopamine on these variables in controls (P ≥ 0.7). Hyperoxia lowered ventilation in HF (P = 0.01), but not in controls (P = 0.9), indicating suppression of the peripheral chemoreceptors in HF. However, no decrease of total peripheral resistance index was observed in HF. As expected, HG increased heart rate, ventilation, and brachial conductance of the nonexercising arm in controls and HF patients. During dopamine infusion, there were no changes in mean arterial pressure, heart rate, or ventilation responses to HG in either group (P ≥ 0.26); however, brachial conductance increased with dopamine in the control group (P = 0.004), but decreased in HF (P = 0.02). Our findings indicate that the peripheral chemoreceptor contributes to cardiovascular control at rest in HF patients and during exercise in risk-matched controls.

Cardiac function; vascular function; dopamine

THE ACTIVITY AND SENSITIVITY of the peripheral chemoreceptors (i.e., carotid chemoreceptor) is enhanced in chronic heart failure (HF) (22, 23, 50, 61, 63). In HF patients, enhanced peripheral chemosensitivity is associated with increased mortality (22, 50). The physiological significance of enhanced peripheral chemoreceptor activity in HF patients is unclear; however, previous work in experimental HF has shown that inhibition of the peripheral chemoreceptor leads to peripheral vasodilation and improvement in cardiac function (61). Furthermore, these changes can be blocked by the administration of phentolamine (i.e., adrenergic blockade), indicating that they are due to a reduction in sympathetic nerve activity (SNA) (61). Indeed, increased peripheral chemoreceptor activity/sensitivity in experimental HF leads directly to higher SNA (63), and elevations in sympathetic activity are also associated with greater mortality in HF patients (2, 8, 19). Combined, these findings would suggest that enhanced peripheral chemoreceptor activity or sensitivity increases sympathetic vasoconstrictor outflow in HF patients, reducing cardiac output and peripheral blood flow; however, this has not been examined in clinical HF. Importantly, standard medical management for HF includes medications such as β-blockers and angiotensin receptor blockers (ARBs) (39). In clinical and preclinical studies, these medications have been shown to have effects on the carotid body and/or ventilation (3, 32, 71), and thus it is unclear if previous conclusions from animal models of HF that have suggested that the peripheral chemoreceptor plays an important role in cardiovascular control translate to appropriately managed HF patients.

Moderate doses of dopamine (5 μg·kg⁻¹·min⁻¹) inhibit the peripheral chemoreceptor in HF patients, as demonstrated by a reduction in minute ventilation (V˙E) (68), while low dose dopamine (2 μg·kg⁻¹·min⁻¹) has been shown to cause peripheral vasodilation and lower blood pressure in critically ill patients, which has been assumed to be secondary to stimulation of peripheral dopaminergic receptors (9, 18, 24, 69). However, vasodilation from intravenous dopamine has not been a consistent finding in conditions of low peripheral chemoreceptor activity/sensitivity (6, 38) nor at rest in healthy controls (5, 46, 60). Perhaps a more active or sensitive peripheral chemoreceptor, as seen in many HF patients (12, 50), is necessary to observe a benefit from low-dose dopamine infusion. Accordingly, the first goal of this study was to determine whether peripheral chemoreceptor inhibition at rest improved vascular and cardiac function in HF patients and controls.

HF is also characterized by a potentiated sympathetic response to handgrip (HG) exercise (40, 41, 47), and the peripheral chemoreceptor has been shown to contribute to sympathetic vasoconstrictor outflow during HG exercise and leg extension exercise in young, healthy humans (17, 60, 62). Similarly, the peripheral chemoreceptor appears to contribute to sympathetic output during treadmill exercise in healthy and HF animals (61). However, the role of the peripheral chemoreceptor in sympathetic output during exercise has yet to be confirmed in HF patients or in an older population. Therefore,
a second goal of the study was to determine whether peripheral chemoreceptor inhibition during exercise resulted in greater peripheral vasodilatation in HF patients. We hypothesized that 1) inhibition of the peripheral chemoreceptor at rest would decrease \( V\dot{E} \) while increasing cardiac output and stroke volume in HF patients; and 2) inhibition of the peripheral chemoreceptor during HG exercise would improve peripheral conductance in both at-risk but otherwise healthy controls [i.e., American Heart Association (AHA)/American College of Cardiology (ACC) class A patients (27)] and HF patients, with a greater effect observed in HF.

To determine the role of the peripheral chemoreceptor in cardiovascular and respiratory regulation of appropriately medicated HF patients, and to translate previous animal work, we inhibited the peripheral chemoreceptor at rest with either low-dose dopamine or hyperoxia while evaluating hemodynamics and peripheral blood flow. In addition, we assessed hemodynamics and peripheral blood flow during HG exercise, with or without peripheral chemoreceptor inhibition with dopamine.

Lastly, as a tertiary goal, in an attempt to determine resting peripheral chemoreceptor sensitivity in both groups, participants underwent a resting hypoxia trial while cardiorespiratory data were collected. Stable HF patients and control participants with similar cardiovascular risk factors [i.e., at least one of the following: body mass index (BMI) >30, hypertension, dyslipidemia] were examined in an attempt to isolate the effects of the HF itself.

### MATERIALS AND METHODS

**Ethical approval and participant description.** The study was approved by the University of Alberta Health Research Ethics Board (Biomedical Panel), and all participants provided written, informed consent. Clinically stable HF patients (n = 11) were recruited from the Heart Function Clinic at the University of Alberta hospital and the collaborative Alberta HEART study (http://albertaheartresearch.ca/ the-study/). Controls (ACC/AHA class A subjects; n = 10) were recruited from the Chest Pain Clinic at the University of Alberta hospital, the collaborative Alberta HEART study, or the general population (Table 1). Patients with renal dysfunction were excluded from the study. All participants refrained from exercise, alcohol, and caffeine for 12 h before the study. All subjects underwent a standard cardiopulmonary exercise test (Vmax system; VIASYS Products) under supervision of a cardiologist to ensure that patients were stable for hypoxia or dopamine administration, followed by an experimental session conducted on a separate day (described below). Overnight sleep monitoring was performed in each participant (ApneaLink Plus, ResMed, San Diego, CA; Sleep FX, St. Albert, Alberta, Canada) and was defined as a respiratory index of >10 (respiratory index: control: 17 ± 4 number of arousals/h; HF: 14 ± 3 number of arousals/h; \( P = 0.5 \)).

**Experimental protocol.** Before all experimental data collection, an intravenous catheter, connected to a saline infusion pump (Alaris, CareFusion, San Diego, CA) to maintain patency, was inserted into the antecubital vein of the right arm. Participants then performed a HG maximum voluntary contraction (MVC; left hand) using a HG dynamometer (G100; Biometrics, Ladysmith). Visual feedback was provided to ensure participants maintained 40% throughout subsequent trials. Four trials were performed in random order for each participant.

1) Normoxia: Five minutes of resting normoxia (baseline) that was followed by 2 min of 40% MVC static HG exercise in normoxia.

2) Dopamine: While the subjects were breathing normoxia throughout, data were recorded for 2 min (preinfusion). Then, intravenous dopamine HCl infusion (2 \( \mu \)g.kg\(^{-1}.\)min\(^{-1} \); Hospira) was initiated using an automated constant-infusion pump. Participants were not aware of when the dopamine infusion started. Of note, dopamine HCl does not cross the blood-brain barrier (reviewed in Ref. 72) and, therefore, would not act directly on central chemoreceptors. This dose was selected as it has been previously shown to inhibit the peripheral chemoreceptor (as evidenced by a reduction in \( V\dot{E} \)), while not affecting hemodynamics in young healthy individuals (5). Following a 5-min wash-in period, 5 min of resting data were obtained (baseline). Participants subsequently performed 2 min of 40% MVC static HG exercise.

3) Hyperoxia: Participants breathed normoxia for 5 min (baseline) followed by 2 min of resting hyperoxia (infrared fraction of \( O_2 \) = 1.0). Hyperoxia was used, as it has previously been shown to inhibit the peripheral chemoreceptor (60, 62). HG exercise was not performed during hyperoxia administration.

4) Hypoxia: Participants breathed normoxic air for 3 min (baseline), followed by a change of inhaled gases to achieve arterial saturation of \( O_2 \) from pulse oximetry (\( SpO_2 \)) of 90% for 3 min and \( SpO_2 \) of 85% for 3 min. Inspired oxygen was modulated using an air-oxygen or air-nitrogen blender system. Importantly, this method of determining the ventilatory response to hypoxia is different than that used by other groups (44, 50–52) due to concurrent studies in this laboratory that investigate patients with respiratory disease. This trial was conducted in an attempt to determine peripheral chemoreceptor sensitivity, which was calculated by determining the slope of the relationship between \( V\dot{E} \) and \( SpO_2 \) in room air, \( SpO_2 \) of 90%, and \( SpO_2 \) of 85%. HG exercise was not performed during hypoxia administration.

Note: The ventilatory response to hypoxia was not investigated during the dopamine infusion because of cardiologist concerns for patient safety.

All trials were separated by at least 5 min of rest (until cardiorespiratory variables returned to baseline), while at least a 10-min wash-out period was given after each dopamine trial. One-minute averages of cardiovascular and respiratory measurements were obtained, and the last minute of each condition is reported. Due to
technological limitations, stroke volume index (SV\textsubscript{i}), cardiac index (Q\textsubscript{i}), and total peripheral resistance index (TPR\textsubscript{i}) were measured during the second minute of each condition, and brachial conductance was measured thereafter. In addition, with the goal of evaluating the immediate response to hyperoxia, respiratory data were also reported 2 min into breathing hyperoxia.

Cardiorespiratory measurements. Data were recorded and analyzed using a Powerlab data acquisition system (Powerlab 16/30) and LabChart 7.2 software (ADInstruments). V\textsubscript{E} was measured with a pneumotachometer (3700 series; Hans Rudolph, Shawnee, KS), and end-tidal CO\textsubscript{2} and O\textsubscript{2} were determined using gas analysis (CD-3A and S-3A; AEI Technologies, Pittsburgh, PA). Inspired gas was humidified (HC 150; Fisher and Paykel Healthcare). Sp\textsubscript{O2}, was estimated using a forehead pulse-oximeter (N-595; Coviden, Mansfield, MA). A single-lead ECG was used to determine heart rate (HR) from the R-R interval (BioAmp; ADInstruments), and blood pressure was determined using finger photoplethysmography (Finometer Midi, Amsterdam, the Netherlands). Blood pressure was calibrated at regular intervals using a manual measurement.

Doppler ultrasound. Brachial conductance in the nonexercising arm and SV\textsubscript{i} were obtained using pulsed-wave Doppler ultrasound (Vivid q, GE Healthcare, Burnaby, BC, Canada). The quadrature output of the ultrasound spectrum of brachial blood flow velocity was demodulated using a Multigon Doppler system (model 500M; Multigon, Yonkers, NY), which, in turn, provided a continuous analog signal of the forward and backward velocities, which were then integrated into the Powerlab system (56, 60). Aortic blood flow velocity was determined by integrating the outer envelope of five heartbeats. In both cases, the average velocity was multiplied by the cross-sectional area of the brachial artery or left ventricular outflow tract (two-dimensional ultrasound) to get volume. Brachial volume was multiplied by 60 for brachial flow (ml/min). Stroke volume was multiplied by HR for cardiac output (ml/min) and normalized to body surface area [Dubois formula (15)]. Brachial flow was normalized to arm volume. Arm volume was calculated using the volume of a truncated cone: \[ V = h(C_1^2 + C_2^2 + C_3^2)/12\pi, \] where \( C_1 \) is the circumference around the wrist, \( C_2 \) is the circumference around the forearm, and \( h \) is the distance between the two (4, 16, 53, 65). Brachial conductance was calculated by brachial flow/mean arterial pressure (MAP).

Statistical analysis. For all inferential analyses, the probability of type I error was set at 0.05. Values are presented as means \( \pm \) SE. Between-group comparisons of baseline characteristics were evaluated by unpaired t-test or \( \chi^2 \) testing, where appropriate. A three-way repeated-measures ANOVA was used to evaluate the effect of saline vs. intravenous dopamine (factor A) at rest and during exercise (repeated factor) in HF and controls (fixed factor). Likewise, a two-way repeated-measures ANOVA was used to evaluate the effect of normoxia vs. hyperoxia (or normoxia vs. hypoxia; repeated factor) at rest in HF and controls (fixed factor). To interpret the group \( \times \) condition \( \times \) time interaction, follow-up one-way repeated-measures ANOVAs were conducted where appropriate, isolating the within-subject factors one at a time (i.e., condition and then time). Equal variance was present for all tests. Statistical tests were completed using either SPSS (version 21, IBM, Armonk, NY) or SigmaPlot 12.0 (Systat Software, San Jose, CA).

RESULTS

Patient characteristics are reported in Table 1. Risk-matched controls and HF patients were well matched for age, sex, prevalence of sleep apnea, and other risk factors. As expected, HF patients had lower ejection fraction and peak O\textsubscript{2} consumption (V\textsubscript{O2peak}). Neither group showed evidence of airflow obstruction.

RESPIRATORY RESPONSES TO HG EXERCISE WITH OR WITHOUT DOPAMINE. HG exercise increased MAP, HR, and V\textsubscript{E} (Fig. 2) and brachial conductance in both groups (Fig. 3). The dopamine infusion did not change the responses of MAP, HR, or V\textsubscript{E} to HG exercise (Fig. 2). Both groups experienced an increase in systolic and diastolic blood pressure during HG exercise (Table 3). During the dopamine infusion and HG, there was an increase of brachial conductance in controls (Fig. 3A) and a decrease of brachial conductance in HF (Fig. 3B). Combined, these results indicate that inhibition of the peripheral chemoreceptor during exercise increased vascular conductance in the control group, but resulted in lower vascular conductance in HF patients.

Cardiorespiratory responses to hypoxia. As expected, hypoxia increased V\textsubscript{E} in both groups; however, the ventilatory response to hypoxia (\( \Delta V\textsubscript{E}/\Delta P\textsubscript{O2} \)) was similar in HF compared with controls. Hypoxia resulted in increased MAP and HR in both groups; however, brachial conductance was unaffected by hypoxia in both HF and controls (Table 4).

DISCUSSION

Peripheral chemoreceptor inhibition with either low-dose dopamine or hyperoxia reduced V\textsubscript{E} in HF patients, but not controls, indicating that the peripheral chemoreceptor is tonically active at rest in HF but not in older people with one or more cardiovascular risk factor(s) (AHA/ACC class A patients). Low-dose dopamine also improved Q\textsubscript{i} and SV\textsubscript{i} in HF patients at rest, likely a result of lower TPR\textsubscript{i}. These findings translate our previous work in experimental HF (61) and indicate that the peripheral chemoreceptor likely contributes to cardiovascular regulation at rest in stable, pharmacologically managed HF patients. Consistent with previous work in young, healthy subjects and healthy animals (60, 61), peripheral chemoreceptor inhibition with dopamine during HG exercise in our control group increased brachial conductance, suggesting a reduction in SNA. However, contrary to previous animal work (61), and our original hypothesis, peripheral chemoreceptor inhibition with dopamine did not improve cardiovascular function during exercise in HF. Nonetheless, these findings indicate that...
the peripheral chemoreceptor does play a role in cardiovascular regulation in HF at rest and is a potential target for treatment in HF.

Surprisingly, when comparing controls and HF patients, the ventilatory response to hypoxia (\(\Delta V_e/\Delta SpO_2\)) and the ventilatory response relative to CO2 production during exercise [\(V_e/\text{CO}_2\) production (\(V_{\text{CO}_2}\))] were not different between groups. These findings are in contrast to other work that showed both an increased ventilatory response to hypoxia (52) and an increased \(V_e/V_{\text{CO}_2}\) (44, 52) in HF compared with controls. The similarities in both the ventilatory responses to hypoxia and exercise between our HF group and controls could be due to a variety of reasons. First, our HF group was relatively fit, and their \(V_{\text{O}_2}\text{peak}\) corresponded to a previously published group of HF patients who had a similar \(V_e/V_{\text{CO}_2}\) slope and improved survival compared with those HF patients with a lower \(V_{\text{O}_2}\text{peak}\) and higher \(V_e/V_{\text{CO}_2}\) (25). Second, we used a different hypoxia protocol compared with others (44, 50 – 52), which may have resulted in a different response. Third, the lack of between-group difference in ventilatory responses in the present study may be explained by the risk-matching of the HF and control groups. The control group in the present study had some cardiovascular risk factors (i.e., hypertension, sleep apnea, high BMI, high cholesterol) that could be responsible for increasing their ventilatory responses to hypoxia/exercise. Hypertension, mild to moderate obesity, and sleep apnea have all been linked with higher \(V_e\) in hypoxia (21, 43, 66), and 9/10 of our control participants had at least one of these risk factors. Finally, the lack of difference in ventilatory responses between risk-matched controls and HF patients could be due to pharmaceutical management (e.g., \(\beta\)-blockers and ARBs). While previous investigations have found that the ventilatory response to hypoxia or exercise is enhanced in HF (7, 28, 50), some of the older investigations were performed in patients not receiving either \(\beta\)-blockade or angiotensin II blockade therapy. Indeed, a more recent study in HF men who were managed with optimal pharmacotherapy found no difference in the ventilatory response to hypoxia in these patients compared with a control group (44). Both \(\beta\)-blockade and ARBs have been shown to reduce \(V_e/V_{\text{CO}_2}\) during exercise in HF patients (29, 71), which suggests that these medications may affect chemosensitivity. Similarly, angiotensin II has also been shown to affect peripheral chemoreceptor sensitivity, without modulating peripheral chemoreceptor basal activity in HF (33). Considering 10 of 11 HF patients were on angiotensin converting enzyme inhibitors or ARBs, this may have reduced the ventilatory response to hypoxia in these patients. Together, these previous studies would suggest that \(\beta\)-blockers and ARBs appear to
reduce chemosensitivity. Despite no evidence of enhanced ventilatory response to hypoxia in our HF patients, our findings indicate that, even with optimal pharmacological management, enhanced tonic peripheral chemoreceptor activity still contributes to cardiovascular regulation in HF.

**Cardiorespiratory and autonomic responses to dopamine at rest.** Dopamine has been used to improve renal function in HF (9, 18, 24, 69); however, cardiovascular improvements are not always noted (31, 42). Dopamine is thought to work via direct stimulation of dopamine-1 receptors in the peripheral and renal vasculature (26, 64), yet dopamine is also known to suppress peripheral chemoreceptor activity in HF patients (68). Suppression of peripheral chemoreceptor activity would reduce sympathetic output and, therefore, increase renal blood flow and cardiac function. Therefore, we suggest that some of the cardiovascular benefits that are traditionally ascribed only to stimulation of the peripheral dopamine receptors from low-dose dopamine treatment in HF could also be at least partially due to peripheral chemoreceptor inhibition.

Indeed, in the present study, it was observed that, pharmacologically managed HF patients at rest, dopamine suppressed activity of the peripheral chemoreceptor (as shown by the reduction in $V_E$) and, therefore, reduced sympathetic outflow (as shown by a reduction in total peripheral resistance) and increased cardiac function. It is acknowledged that any direct peripheral vasodilatory actions of dopamine (via direct stimulation of dopamine-1 vascular receptors) could also contribute to a reduction in total peripheral resistance and, therefore, an increase in cardiac output; however, it would be assumed that any direct peripheral vascular effects of dopamine would have also been observed in risk-matched controls. It is possible that dopamine did not have a direct vascular effect in the controls due to limited baseline vasoconstrictor outflow. Nevertheless, the combined observations that dopamine reduces $V_E$ and resulted in vasodilation in HF (as measured by TPR), while controls showed no reduction in $V_E$ and no vasodilation, strongly suggest that the cardiovascular effects with dopamine in HF are secondary to peripheral chemoreceptor inhibition.

A reduction of sympathetic outflow could lead to lower mortality, improved oxygen delivery, and improved exercise tolerance in HF. While our patients did not have enhanced ventilatory responses to steady-state hypoxia at rest, our findings would indicate that resting basal peripheral chemoreceptor activity is indeed elevated in HF patients relative to risk-matched controls, leading to enhanced resting sympathetic output. These findings would support recent work showing that carotid denervation in experimental HF reduced peripheral chemoreceptor activity/sensitivity and SNA, while improving cardiac function and survival (11, 36), and a recent case study showing that unilateral denervation of the carotid body in a HF patient improved exercise capacity and autonomic balance (45).

**Cardiorespiratory responses to hyperoxia at rest.** As both dopamine and hyperoxia inhibit the peripheral chemoreceptor, we anticipated similar results from our dopamine infusion and 2 min of inhaled hyperoxia. Indeed, $V_E$ in HF was reduced with both treatments, indicating that the peripheral chemoreceptor was active at rest in HF; however, a reduction in total peripheral resistance and an increase in cardiac output in the HF patients were only observed with dopamine. Importantly, the integrated cardiorespiratory responses to inhaled hyperoxia are complicated. As an example, prolonged hyperoxia can act as a central stimulant (10), which would potentially increase vascular resistance and impair cardiovascular function, which could help to explain why no changes in hemodynamics were seen with hyperoxia compared with dopamine infusion. Indeed, previous work has shown that hyperoxic breathing results in an increase in forearm vascular resistance, as well as impaired left ventricular function in both controls and HF (35). These data further highlight the cardiorespiratory complexity of hyperoxia, and similar to Mak et al. (35), we suggest that caution should be used in the administration of prolonged high inspired $O_2$ fractions in HF.

**Cardiorespiratory responses to HG exercise with or without dopamine.** Alves et al. (1) and Soares-Miranda et al. (59) found that HG exercise in controls and HF patients increased forearm vascular conductance in the nonexercising arm. Similarly, we also observed an increase in brachial conductance during HG exercise in both HF patients and controls. Soares-Miranda et al. and Alves et al. both found impaired vasodilation during exercise in HF patients compared with the control group; however, in the present study, there was no significant difference in the brachial conductance response to exercise between the control group and the HF patients. The control group in our study may have had attenuated brachial vasodilation during exercise due to the presence of cardiovascular risk factors and/or the use of vasoactive medications in our subjects. Soares-Miranda et al. investigated healthier controls who were not medicated for cardiovascular disease, which could have led to greater vascular responsiveness in their control group. Similarly, Alves et al. investigated younger controls and patients (40–45 yr old; none was prescribed $\beta$-blocker medication), which could also have led to greater vascular responsiveness.
Shoemaker et al. (57) suggested that the inability of HF patients to increase forearm vascular conductance in response to exercise is due to increased skeletal muscle metabolism rather than vasodilatory dynamics (i.e., lactate and H+ concentration were higher after HG exercise in HF). Indeed, most studies have found an enhanced metaboreflex (47–49, 54, 58) and, similarly, an enhanced mechanoreflex (40), in HF. The peripheral chemoreceptor has been shown to play a role in the sympathetic control of cardiovascular function during exercise (20, 55, 61, 70); however, the relative contribution of the peripheral chemoreceptor to total sympathetic control during exercise appears to be lower in HF compared with health (61). In the

Fig. 2. Effect of the low-dose dopamine infusion on responses to handgrip exercise in controls (left) and HF (right) for mean arterial pressure (A and D), heart rate (B and E), and ventilation (C and F). Values are means ± SE. *Significant main effect of exercise ($P < 0.001$). #Significant difference between groups ($P < 0.004$).

Fig. 3. Effect of the low-dose dopamine infusion on brachial conductance during handgrip exercise in controls (A) and HF (B). Values are means ± SE. *Significant effect of exercise ($P = 0.006$). †Significant increase in controls and a significant decrease in HF ($P = 0.035$).
present study, we did not find evidence of reduced sympathetic output during dopamine infusion during exercise in HF. In fact, we observed lower brachial conductance with dopamine. To help clarify these results, further studies investigating the interactions of autonomic reflexes during exercise in HF are warranted.

Cardiorespiratory responses to hypoxia. As discussed above, the ventilatory response to hypoxia was comparable between controls and HF patients. Similar to our findings, Di Vanna et al. (14) found no difference between controls and HF in the cardiorespiratory response to steady-state hypoxia (SpO2 ~84% in both groups); however, they observed a significant increase of forearm vascular conductance in controls but not in HF. In the Di Vanna study, the controls were unmedicated, had lower BMI (24 ± 1 kg/m²), higher V02peak (28 ± 2 ml·min⁻¹·kg⁻¹), and were younger (46 ± 3 yr) compared with the present study, and, importantly, age (13), obesity (30), and low maximum O2 consumption (34) are all associated with lower plasma nitric oxide availability [the primary contributor to hypoxic vasodilation (37)]. Therefore, our controls and HF patients may have had lower nitric oxide bioavailability and, therefore, impaired hypoxic vasodilation relative to previous work.

Limitations. Previous work examining chemosensitivity in HF patients has not investigated the prevalence of sleep apnea (28, 44, 50, 52). We found a surprisingly high prevalence of sleep apnea in both our control and HF groups; however, as the prevalence was similar between controls and HF, the differences observed with respect to the effect of peripheral chemoreceptor inhibition on cardiovascular control at rest would not

Table 3. Responses to handgrip exercise with or without dopamine infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Condition</th>
<th>Resting Baseline</th>
<th>Handgrip</th>
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</thead>
<tbody>
<tr>
<td>SpO2, %</td>
<td>Control</td>
<td>Normoxia</td>
<td>97.4 ± 0.7</td>
<td>97.9 ± 0.8</td>
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<tr>
<td></td>
<td>Dopamine</td>
<td></td>
<td>97.2 ± 0.5</td>
<td>97.4 ± 0.7</td>
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<tr>
<td></td>
<td>HF</td>
<td>Normoxia</td>
<td>96.7 ± 0.7</td>
<td>97.1 ± 0.7</td>
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<td></td>
<td></td>
<td>Dopamine</td>
<td>96.8 ± 0.6</td>
<td>97.3 ± 0.6</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>Control</td>
<td>Normoxia</td>
<td>130.5 ± 6.5</td>
<td>159.2 ± 10.2*</td>
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<td></td>
<td></td>
<td>Dopamine</td>
<td>131.9 ± 6.4</td>
<td>150.7 ± 9.2*</td>
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<tr>
<td></td>
<td>HF†</td>
<td>Normoxia</td>
<td>117.9 ± 5.8</td>
<td>125.4 ± 9.1*</td>
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<td></td>
<td></td>
<td>Dopamine</td>
<td>108.8 ± 4.7</td>
<td>123.4 ± 7.9*</td>
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<td>Diastolic blood pressure, mmHg</td>
<td>Control</td>
<td>Normoxia</td>
<td>78.2 ± 3.3</td>
<td>88.2 ± 4.4*</td>
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<td></td>
<td></td>
<td>Dopamine</td>
<td>81.6 ± 3.6</td>
<td>93.3 ± 3.8*</td>
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<tr>
<td></td>
<td>HF†</td>
<td>Normoxia</td>
<td>61.1 ± 2.9</td>
<td>66.2 ± 4.1*</td>
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<tr>
<td></td>
<td></td>
<td>Dopamine</td>
<td>60.1 ± 2.8</td>
<td>67.3 ± 3.8*</td>
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</table>

Values are means ± SE. *Significant main effect of exercise (P = 0.002). †Significant difference between groups (P < 0.001).

Table 4. Responses to hypoxia

<table>
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<tr>
<th>Variable</th>
<th>Group</th>
<th>Baseline</th>
<th>90% SpO2</th>
<th>85% SpO2</th>
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</thead>
<tbody>
<tr>
<td>Ventilation, l/min</td>
<td>Control</td>
<td>6.5 ± 0.7</td>
<td>8.5 ± 0.6§</td>
<td>9.1 ± 0.9†</td>
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<tr>
<td></td>
<td>HF</td>
<td>7.7 ± 0.6</td>
<td>8.9 ± 0.8§</td>
<td>10.8 ± 1.3†</td>
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<tr>
<td>SpO2, %</td>
<td>Control</td>
<td>97.3 ± 0.6</td>
<td>90.3 ± 0.5§</td>
<td>85.3 ± 0.3†</td>
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<tr>
<td></td>
<td>HF</td>
<td>97.7 ± 0.8</td>
<td>88.8 ± 0.4§</td>
<td>84.6 ± 0.6†</td>
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<tr>
<td>ΔV̇E/ΔSpO2, l·min⁻¹·%⁻¹</td>
<td>Control</td>
<td>0.21 ± 0.03</td>
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<tr>
<td></td>
<td>HF</td>
<td>0.24 ± 0.07</td>
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<td></td>
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<tr>
<td>Respiratory rate, breaths/min</td>
<td>Control</td>
<td>11.0 ± 1.5</td>
<td>10.0 ± 1.3</td>
<td>11.4 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>15.3 ± 1.6</td>
<td>14.2 ± 1.4</td>
<td>15.6 ± 1.3</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>Control</td>
<td>38.7 ± 1.8*</td>
<td>35.6 ± 2.3</td>
<td>32.9 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>34.2 ± 1.6*</td>
<td>30.5 ± 2.0</td>
<td>29.8 ± 2.1</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>Control</td>
<td>104.9 ± 2.9</td>
<td>60.3 ± 2.3§</td>
<td>52.5 ± 2.7‡</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>105.8 ± 3.1</td>
<td>64.3 ± 7.3§</td>
<td>56.5 ± 6.8‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>Control</td>
<td>95.5 ± 4.4</td>
<td>97.3 ± 4.1</td>
<td>99.1 ± 4.6‡</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>85.5 ± 6.0</td>
<td>87.3 ± 6.0</td>
<td>87.5 ± 6.1‡</td>
</tr>
<tr>
<td>Stroke index, ml/m²</td>
<td>Control</td>
<td>56.3 ± 4.2*</td>
<td>60.7 ± 4.2</td>
<td>61.3 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>45.2 ± 5.0</td>
<td>43.2 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Cardiac index, l·min⁻¹·m⁻²</td>
<td>Control</td>
<td>47.8 ± 5.9</td>
<td></td>
<td>44.7 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>2.7 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance index, mmHg·l⁻¹·min⁻¹·m⁻²</td>
<td>Control</td>
<td>3.0 ± 0.4</td>
<td></td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>37.8 ± 3.8</td>
<td></td>
<td>36.9 ± 3.8</td>
</tr>
<tr>
<td>Brachial conductance, ml·min⁻¹·mmHg⁻¹·cm⁻³</td>
<td>Control</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>Control</td>
<td>129.8 ± 6.5*</td>
<td>132.4 ± 6.2</td>
<td>136.8 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>116.4 ± 8.1*</td>
<td>120.6 ± 8.8</td>
<td>121.2 ± 8.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>Control</td>
<td>77.8 ± 3.3</td>
<td>78.8 ± 3.1</td>
<td>79.6 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>HF</td>
<td>69.6 ± 5.2</td>
<td>70.5 ± 5.1</td>
<td>70.3 ± 5.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. ΔV̇E/ΔSpO2, ventilatory response to hypoxia (control: n = 7; HF: n = 9). *Significant difference between baseline and other time points (P < 0.05). †Significant difference between 90% and other time points (P < 0.01). ‡Significant difference between 85% and other time points (P < 0.01). §Significant difference between baseline and 85% (P < 0.05).
be explained by underlying sleep apnea in HF. Considering the frequent occurrence of sleep apnea in HF, and the potential additive effects of HF and sleep apnea on autonomic/vascular deterioration, future studies should examine the interaction of sleep apnea, peripheral chemoreceptor activity/sensitivity, and HF.

Our cohort of HF patients was on optimal evidence-based medical therapy, and it would have been interesting to investigate a group of HF patients who were newly diagnosed and, therefore, not taking standard HF pharmacotherapy, as pharmaceutical use could increase the variance of responses. Furthermore, few studies have compared the cardiorespiratory responses of ischemic vs. nonischemic HF; however, it might be wise to consider in future studies. If there are indeed differences between these two groups of HF, then the inclusion of both groups may have also increased the variance of the cardiorespiratory responses in the present study. Similarly, an investigation into the responses of a group of patients with more severe HF could reveal more drastic differences between groups, as severe HF has been linked with lower VO2peak (25) and higher V̇O2/V̇CO2 (25), and the severity of HF can modulate the renal effects of a moderate dose of dopamine (67).

We were unable to obtain measurements of SNA throughout the entire protocol due to technical difficulties and due to the need of patients to urinate, particularly after the dopamine infusion. However, by investigating the end-organ response via observations of both cardiac output and peripheral vascular conductance of the nonexercising arm, the functional significance of peripheral chemoreceptor inhibition both at rest and during HG exercise was evaluated in the present study. Technical limitations also prevented measurement of regional blood flow at rest and during the HG exercise trials; however, measurements of both splanchnic and renal blood flow would have been beneficial to determine whether there was any differential sympathetic output during exercise or hypoxia. We were also limited in our ability to concurrently measure Q̇SV, and brachial conductance, as we used the same ultrasound machine for these measurements.

Significance and perspectives. We found that low-dose dopamine improved Q̇ and SV in HF patients at rest, but not in older adults with one or more cardiovascular risk factor(s), and we suggest that this is at least partially due to inhibition of the peripheral chemoreceptor. These results translate previous animal work and demonstrate that the peripheral chemoreceptor is active and plays a role in resting cardiovascular regulation in clinically stable HF patients on optimal medical therapy. This tonic activity of the peripheral chemoreceptor in HF would contribute to enhanced resting SNA, and both higher peripheral chemoreceptor activity and higher SNA have been associated with greater mortality (2, 8, 19, 50). Further studies are needed to examine interventions, such as an exercise training regime, that could chronically reduce peripheral chemoreceptor activity in HF and thus improve survival.

In addition, future studies that use dopamine to investigate renal blood flow and hemodynamics should consider the effects of peripheral chemoreceptor activity. If low-dose dopamine elicits its primary beneficial effects via suppression of the peripheral chemoreceptor rather than via direct effects on dopamine receptors in the kidney (as traditionally believed), perhaps low-dose dopamine alone can be revisited as a pharmacological treatment for HF patients with enhanced peripheral chemoreceptor activity and for any other patients with enhanced peripheral chemoreceptor activity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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